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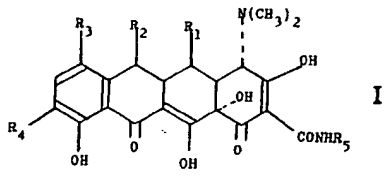
(54) TETRACYCLINES

(71) We, SOCIETA FARMACEUTICI ITALIA S.P.A., a body corporate organised and existing under the laws of Italy, of 1/2 Largo Guido Donegani-1 20121 Milan, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to tetracycline derivatives substituted in at least one of the 7, 9 or N^2 positions by alkyl or methylthioalkyl groups. These tetracycline derivatives are of therapeutic interest.

The invention provides a process comprising reacting, in the presence of a strong acid and in the absence of water, a tetracycline derivative of the general formula



I

wherein

R_1 represents a hydrogen atom, a hydroxy group or an acyloxy group having from 1 to 4 carbon atoms;

R_2 represents a hydrogen atom or a methyl group;

R_3 represents a hydrogen atom when R_2 represents a methyl group or otherwise represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a methylthioalkyl group having from 2 to 5 carbon atoms or a dimethylamino group;

R_4 represents a hydrogen atom when R_3 represents a dimethylamino group or otherwise represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms or a methylthioalkyl group having from 2 to 5 carbon atoms; and

R_5 represents a hydrogen atom, with a sulphide of the general formula

$$CH_3—S—CHRCl \qquad II$$

wherein R represents a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms, thereby to introduce according to the following stipulations one or more methylthioalkyl substituents of the formula(e)

$$CH_3—S—CHR—$$

wherein R is as above defined:

(a) if R_2, R_3 and R_4 all represented hydrogen atoms, for one of R_3 and R_4, both of R_5 and R_4 or all of R_3, R_4 and R_5,

(b) if R_2 represented a methyl group and R_4 represented a hydrogen atom, for R_4 or both of R_4 and R_5,

(c) if R_2 represented a methyl group and R_4 did not represent a hydrogen atom, for R_5,

(d) if R_2 and R_3 both represented hydrogen atoms and R_4 did not represent a hydrogen atom, for R_3 or both of R_3 and R_5,

(e) if R_3 represented a dimethylamino group, for R_5,

(f) if R_3 represented neither a dimethylamino group nor a hydrogen atom and R_4 represented a hydrogen atom, for R_4 or both of R_4 and R_5,

(g) if R_3 represented neither a dimethylamino group nor a hydrogen atom and R_4 did not represent a hydrogen atom, for R_5,

and either isolating the methylthioalkyltetracycline derivative or demethylthionating it by refluxing it in a solvent with Raney nickel to give the corresponding alkyl-tetracycline derivative (in which the or each alkyl substituent is of the formula RCH_2— wherein R is as above defined).

The tetracycline derivatives produced by

the process according to the invention are those of the general formula I

wherein

R_1 represents a hydrogen atom, a hydroxy group or an acyloxy group having from 1 to 4 carbon atoms;

R_2 represents a hydrogen atom or a methyl group;

R_3 represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a methylthioalkyl group having from 2 to 5 carbon atoms or a dimethylamino group; and

R_4 and R_5 each represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms or a methylthioalkyl group having from 2 to 5 carbon atoms;

with the provisos that R_3 and R_4 do not simultaneously represent hydrogen atoms, that when R_2 represents a methyl group R_3 represents a hydrogen atom and that when R_3 represents a dimethylamino group R_4 represents a hydrogen atom and R_5 does not represent a hydrogen atom.

When the tetracycline derivative used in the reaction already contains one or more alkyl or methylthioalkyl substituent(s) in the 7- and/or 9-position(s) it may have been prepared by a process according to the invention.

The chloroalkyl methyl sulphide reacts rapidly, attacking the 7- and 9-positions of the tetracycline nucleus if they are free and no deactivating substituent is present, or attacking the 2-carbamoyl group if said positions are occupied or if deactivating substituents are present.

The strong acid, which may be organic or inorganic, acts both as condensant and solvent for the tetracycline and sulphide. Suitable strong acids include sulphuric acid, methanesulphonic acid, hydrofluoric acid and trifluoroacetic acid.

The alpha-chloroalkyl methyl sulphide may be used in amounts equivalent to the amount of tetracycline or in excess, and may be added either all at once at the beginning of the reaction or in portions over the course of the reaction. The reaction temperature may vary from 0° to 60°C, but usually one operates at room temperature. The time required for the reaction varies from several hours to several days.

To transform the methylthioalkyl derivatives so obtained into the corresponding alkyl derivatives, the former are submitted to demethylthionation with Raney nickel in a solvent and under refluxing. Lower alcohols such as methanol or ethanol, preferably diluted with water, are suitable as the solvent. The refluxing is preferably carried out for a period of time of from 1 to 18 hours. The Raney nickel catalyst may be eliminated by centrifuging or filtering over Celite (Trade Mark). Trace amounts of Raney nickel not so eliminated may be removed by washing a butanolic solution of the tetracycline derivative with acid.

The course of the reaction may be illustrated with reference to the reactions of sancycline (Formula I,

$$R_1=R_2=R_3=R_4=R_5=H),$$

doxycycline (Formula I,

$$R_1=OH,\ R_2=CH_3,\ R_3=R_4=R_5=H)$$

and minocycline (Formula I,

$$R_1=R_2=R_4=R_5=H,\ R_3=N(CH_3)_2)$$

with chloromethyl methyl sulphide.

Sancycline

With an excess of the chloromethyl methyl sulphide and a long reaction time, the 7,9,N^2-trimethylthiomethyl derivative is obtained. If, however, an equivalent quantity of chloromethyl methyl sulphide is used, an equimolecular mixture consisting of the 7-methylthiomethyl and 9-methylthiomethyl derivatives is obtained. If an excess of chloromethyl methyl sulphide and short reaction times are employed, the 7,9-dimethylthiomethyl derivative is mainly obtained.

9 - *t* - Butyl - sancycline (Formula I,

$$R_1=R_2=R_3=R_5=H,\ R_4=C(CH_3)_3),$$

disclosed in our British Patent Specification No. 1413347, in which the 9-position is already substituted, reacts with an equivalent quantity of chloromethyl methyl sulphide to give 7 - methylthiomethyl - 9 - *t* - butyl - sancycline and with an excess of the chloromethyl methyl sulphide to give 7,N^2 - dimethylthiomethyl - 9 - *t* - butyl - sancycline.

Doxycycline

In this case the 7-position is hindered by the methyl group in the 6-position. Hence the 7-position is not substituted. With an equivalent quantity of chloromethyl methyl sulphide the 9-methylthiomethyl derivative is obtained. With an excess of chloromethyl methyl sulphide the 9,N^2-dimethylthiomethyl derivative is obtained.

Minocycline

In this case the 7-position is already substituted and hinders substitution in the 9-position. The derivative obtained is therefore the N^2-methylthiomethyl derivative.

Our British Patent Specification No. 1413347 describes and claims, inter alia, tetracycline derivatives of the general formula I in which R_1 and R_2 are as hereinbefore

defined, R_3 represents a hydrogen atom or a methyl group, R_4 represents a hydrogen atom or a butyl group and R_5 represents a hydrogen atom, R_3 and R_4 not simultaneously representing hydrogen atoms. With the exception of these compounds, the tetracycline derivatives of the general formula I produced by the process according to the invention are novel compounds and are included within the scope of the invention. The preferred tetracycline derivatives according to the invention are those in which R_1 and R_2 both represent hydrogen atoms (6 - demethyl - 6 - deoxy - tetracycline derivatives), especially those in which R_4 represents a *t*-butyl group (9 - *t* - butyl - 6 - demethyl - 6 - deoxy - tetracycline derivatives) and those in which R_3 represents a dimethylamino group (7 - dimethylamino - 6 - demethyl - 6 - deoxy - tetracycline derivatives). Also preferred are those tetracycline derivatives according to the invention in which R_1 represents a hydroxy group and R_2 represents a methyl group (6 - deoxy - 5 - hydroxy - tetracycline derivatives).

The following Examples illustrate the invention.

EXAMPLE 1

7 - Methylthiomethyl - 6 - demethyl - 6 - deoxy - tetracycline and 9 - methylthiomethyl - 6 - demethyl - 6 - deoxy - tetracycline

1.658 g (4 m mol) of 6 - demethyl - 6 - deoxy - tetracycline were dissolved in 18 ml of trifluoroacetic acid, the mixture was cooled to 0°C, and 0.332 ml (4 m mol) of chloromethyl methyl sulphide were added. After 24 hours at 4°C the solvent was evaporated off under reduced pressure and the residue was transformed into the corresponding hydrochloride by treatment with a solution of hydrogen chloride in anhydrous methanol. 1.8 g of a mixture consisting of 7- and 9-methylthiomethyl derivatives and of the starting material 6 - demethyl - 6 - deoxy - tetracycline were obtained by precipitation from a mixture of *n*-butanol, diethyl ether and petroleum ether.

The 6 - demethyl - 6 - deoxy - tetracycline was readily removed by countercurrent purification in a mixture comprising methyl isobutyl ketone, ethyl acetate, *n*-butanol and McElvain buffer at pH 4.6 in the proportions by volume 480:480:210:1100, and 0.9 g of a mixture comprising the 7- and 9-methylthiomethyl derivatives in an approximately 1:1 ratio was obtained.

Further countercurrent purification and distribution chromatography over Celite gave 7 - methylthiomethyl - 6 - demethyl - 6 - deoxy - tetracycline,

NMR spectrum ($CDCl_3$) on the amphoteric form: 2.01 δ (s, —S—CH_3); 2.49 δ (s, —N(CH_3)$_2$; 3.62 δ (s, —CH_2—S—); 6.78 δ and 7.31 δ (two d, J=9.0 Hz, C_8—*H* and C_9—*H*), U.V. spectrum (CH_3OH—HCl 0.01 N): λ_{max}=222, 268 and 341 nm.,

and 9 - methylthiomethyl - 6 - demethyl - 6 - deoxy - tetracycline,

NMR spectrum ($CDCl_3$) on the amphoteric form: 2.08 δ (s, —S—CH_3); 2.49 δ (s, —N(CH_3)$_2$); 3.74 δ (s, —CH_2—S—); 6.64 δ and 7.38 δ (two d, J=8.0 Hz, C_7—*H* and C_8—*H*), U.V. spectrum (CH_3OH—HCl 0.01 N): λ_{max}=222, 271 and 345 nm.

EXAMPLE 2

7,9 - Di - methylthiomethyl - 6 - demethyl - 6 - deoxy - tetracycline

1 g of 6 - demethyl - 6 - deoxy - tetracycline was dissolved in 9 ml of trifluoroacetic acid, and 3 ml of chloromethyl methyl sulphide were added dropwise. After 15 hours at room temperature, the reaction mixture was treated as in Example 1. 1.3 g of crude product was obtained, and was purified by dissolving it in water and extracting the amphoteric form with chloroform after adjusting the pH to 5.5 with 2 N sodium hydroxide. From the chloroform extracts by concentration and dilution with petroleum ether, 1.2 g of 7,9 - di - methylthiomethyl derivative were obtained.

U.V. spectrum (CH_3OH—HCl 0.01 N): λ_{max}=229, 270 and 345 nm.

NMR spectrum ($CDCl_3$): 2.01 δ (s, —S—CH_3 in 7); 2.07 δ (s, —S—CH_3 in 9); 2.53 δ (s, —N(CH_3)$_2$); 3.62 δ (s, C_7—CH_2—S—); 3.73 δ (s, C_9—CH_2—S—); 7.32 δ (s, C_8—*H*).

EXAMPLE 3

7 - Methyl - 6 - demethyl - 6 - deoxy - tetracycline

A solution of 5 g of 7 - methylthiomethyl - 6 - demethyl - 6 - deoxy - tetracycline hydrochloride (obtained as described in Example 1) in 150 ml of methanol containing 2 ml of water was refluxed for 16 hours under stirring in the presence of 50 g of Raney nickel. The catalyst was removed by centrifuging and washed with methanol acidified with hydrogen chloride. The methanolic solution was evaporated off under reduced pressure and the residue dissolved in butanol.

The butanol solution was washed a number of times with a saturated solution of sodium chloride acidified with hydrochloric acid (pH 1.2) and was then concentrated under reduced pressure. After eliminating a small quantity of sodium chloride, the butanol solution, about 50 ml, was diluted with diethyl ether. 2.5 g of 7 - methyl - 6 - demethyl - 6 - deoxy - tetracycline hydrochloride were obtained. The sample was further purified by

countercurrent distribution as described in Example 1.

U.V. spectrum (CH_3OH—HCl 0.01 N); λ_{max}: 270 and 343 nm.

NMR spectrum ($CDCl_3$—DMSO—d_6, 1:1) carried out on the amphoteric form: 2.17 δ (s, C_7—CH_3); 2.45 δ (s, —$N(CH_3)_2$); 6.71 δ and 7.26 δ (two d, J=9.0 Hz, C_8—*H* and C_9—*H*).

EXAMPLE 4

9 - Methyl - 6 - demethyl - 6 - deoxy - tetracycline

9 - Methyl - 6 - demethyl - 6 - deoxy - tetracycline was obtained starting from 9 - methylthiomethyl - 6 - demethyl - 6 - deoxy - tetracycline (Example 1) and operating as in Example 3.

U.V. spectrum (CH_3OH—HCl 0.01 N) λ_{max}=272 and 345 nm.

NMR spectrum ($CDCl_3$ carried out on the amphoteric form: 2.20 δ (s, C_9—CH_3); 2.47 δ (s, —$N(CH_3)_2$); 6.53 δ and 7.22 δ (two d, J=7.0 Hz, C_7—*H* and C_8—*H*).

EXAMPLE 5

7,9 - Di - methyl - 6 - demethyl - 6 - deoxy - tetracycline

Operating as in Example 3, starting from 7,9 - di - thiomethoxymethyl - 6 - demethyl - 6 - deoxy - tetracycline (obtained as described in Example 2), 7,9 - di - methyl - 6 - demethyl - 6 - deoxy - tetracycline was obtained.

U.V spectrum (CH_3OH—HCl 0.01 N): λ_{max}=273 and 345 nm.

NMR spectrum ($CDCl_3$) carried out on the amphoteric form: 2.17 δ (s, C_7—CH_3); 2.20 δ (s, C_9—CH_3); 2.46 δ (s, —$N(CH_3)_2$); 6.80 δ (s, C_8—*H*).

EXAMPLE 6

7 - Methylthiomethyl - 9 - *t* - butyl - 6 - demethyl - 6 - deoxy - tetracycline

3.6 ml of chloromethyl methyl sulphide were added dropwise at 0°C to a solution of 6 g of 9 - *t* - butyl - 6 - demethyl - 6 - deoxy - tetracycline (obtained as described in Example 1 of British Patent Specification No. 1413347) in 54 ml of trifluoroacetic acid. The reaction mixture was then treated as in Example 2. 4.5 g of 7 - methylthiomethyl - 9 - *t* - butyl - 6 - demethyl - 6 - deoxy - tetracycline were obtained.

U.V. spectrum (CH_3OH—HCl 0.01 N): λ_{max}=234, 271 and 345 nm.

NMR spectrum ($CDCl_3$) carried out on the amphoteric form: 1.40 δ (s, —$C(CH_3)_3$); 2.01 δ (s, —S—CH_3); 3.61 δ (s, —CH_2—S—); 7.26 δ (s, C_8—*H*).

EXAMPLE 7

7 - Methyl - 9 - *t* - butyl - 6 - demethyl - 6 - deoxy - tetracycline

Operating as described in Example 3 and using 6 g of 7 - methylthiomethyl - 9 - *t* - butyl - 6 - demethyl - 6 - deoxy - tetracycline (Example 6), 5.2 g of 7 - methyl - 9 - *t* - butyl - 6- demethyl- 6 - deoxy - tetracycline hydrochloride were obtained.

U.V. spectrum (CH_3OH—HCl 0.01 N): λ_{max}=229, 275 and 345 nm.

NMR spectrum (DMSO—d_6) carried out on the hydrochloride: 1.31 δ (s, —$C(CH_3)_3$); 2.13 δ (s, C_7—CH_3); 2.85 δ (s, —$^{\oplus}NH(CH_3)_2$); 7.28 δ (s, C_8—*H*).

EXAMPLE 8

9 - Methylthiomethyl - α - 6 - deoxy - 5 - hydroxy - tetracycline

30 g of α - 6 - deoxy - 5 - hydroxy - tetracycline hydrochloride were dissolved in 240 ml of trifluoroacetic acid, the mixture was cooled to −10°C, and 15 ml of chloromethyl methyl sulphide were added dropwise. After 15 hours at room temperature, the trifluoroacetic acid was removed under reduced pressure and the residue was transformed into the hydrochloride by treatment with a solution of hydrogen chloride in methanol. Crystallization from a mixture of isopropanol and diethyl ether gave 23.6 g of the hydrochloride of the 9-methylthiomethyl derivative. A sample was further purified by dissolution in water and precipitation of the amphoteric form at pH 5.4 with 2N sodium hydroxide. The precipitate was separated off by centrifuging and recrystallised from a mixture of dimethylformamide, acetone and diethyl ether.

U.V. spectrum (CH_3OH—HCl 0.01 N): λ_{max}=270 and 347 nm.

NMR spectrum (DMSO—d_6) carried out on the amphoteric form: 1.42 δ (d, J=5.0 Hz, C_6—CH_3); 1.96 δ (s, —S—CH_3); 2.49 δ (s, —$N(CH_3)_2$); 3.81 δ (s, —CH_2—S—); 6.87 and 7.45 δ (two d, J=8.0 Hz, C_7—*H* and C_8—*H*).

EXAMPLE 9

9 - Methyl - α - 6 - deoxy - 5 - hydroxy - tetracycline

Operating as in Example 3, from 19.75 g of 9 - methylthiomethyl - α - 6 - deoxy - 5 - hydroxy - tetracycline hydrochloride, (Example 8), 11.84 g of the crude hydrochloride of the 9-methyl derivative were obtained. The product was purified by dissolving it in the minimum amount of boiling water and reprecipitating it by saturating the solution with gaseous hydrogen chloride and subsequent cooling. Crystallization from a mixture of isopropanol and diethyl ether yielded 5.92 g of 9 - methyl - α - 6 - deoxy - 5 - hydroxy - tetracycline hydrochloride.

U.V. spectrum (CH_3OH—HCl 0.01 N): λ_{max}=272 and 345 nm.

NMR spectrum (DMSO—d_6) carried out on the hydrochloride: 1.42 δ (d, J=5.0 Hz, C_6—CH_3); 2.13 δ (s, C_9—CH_3); 2.83 δ (s, $\oplus NH(CH_3)_2$); 6.18 δ and 7.40 δ (two d, J=8.0 Hz, C_7—*H* and C_8—H).

EXAMPLE 10

N^2 - methylthiomethyl - 7 - dimethylamino - 6 - demethyl - 6 - deoxy - tetracycline

8 g of 7 - dimethylamino - 6 - demethyl - 6 - deoxy - tetracycline dihydrochloride were dissolved in 100 ml of trifluoroacetic acid and, while cooling externally with ice, 8 ml of chloromethyl methyl sulphide were added dropwise. After 5 days at room temperature the solution was filtered, diluted with isopropanol and concentrated to a small volume. The product was transformed into the dihydrochloride by adding a solution of hydrogen chloride in methanol. By further concentration and dilution with diethyl ether, 8.79 g of the crude product were obtained. This was transformed into the amphoteric form by dissolving it in water, adjusting the pH to 6.5 with 2N sodium hydroxide and extracting with chloroform. 4.36 g of N^2-methylthiomethyl derivative were obtained by countercurrent purification of the mixture as described in Example 1.

U.V. spectrum (CH_3OH—HCl 0.01 N): λ_{max}=268 and 355 nm.

NMR spectrum ($CDCl_3$) carried out on the amphoteric form: 2.22 δ (s, —S—CH_3); 2.47 δ (s, C_4—$N(CH_3)_2$); 2.59 δ (s, C_7—$N(CH_3)_2$); 4.47 δ (d, J=6 Hz, —CH_2—S—); 6.82 and 7.32 δ (two d, J=9 Hz, C_8—*H* and C_9—*H*).

EXAMPLE 11

N^2 - methyl - 7 - dimethylamino - 6 - demethyl - 6 - deoxy - tetracycline

A solution of 7.26 g of N^2 - methylthiomethyl - 7 - dimethylamino - 6 - demethyl - 6 - deoxy - tetracycline (Example 10) in 200 ml of methanol containing 2 equivalents of hydrogen chloride was refluxed under stirring for 4 hours in the presence of 73 g of Raney nickel. The reaction mixture was filtered over Celite and this was washed with methanol. The methanol solution was then treated as in Example 3. The crude dihydrochloride so obtained was transformed into the amphoteric form at pH 6.5 and purified by countercurrent distribution as described in Example 1.

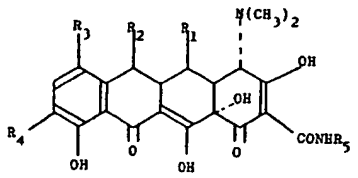
2.40 g of N^2-methyl derivative were obtained and isolated as the dihydrochloride.

U.V. spectrum (CH_3OH—HCl 0.01 N): λ_{max}=265 and 355 nm.

NMR spectrum ($CDCl_3$) carried out on the amphoteric form: 2.47 δ (s, C_4—$N(CH_3)_2$); 2.59 δ (s, C_7—$N(CH_3)_2$); 3.00 δ (d, J=5.2 Hz, CO—NH—CH_3); 6.84 and 7.34 δ (two d, J=9.0 Hz, C_8—*H* and C_9—*H*).

WHAT WE CLAIM IS:—

1. A process comprising reacting, in the presence of a strong acid and in the absence of water, a tetracycline derivative of the general formula



wherein

R_1 represents a hydrogen atom, a hydroxy group or an acyloxy group having from 1 to 4 carbon atoms;

R_2 represents a hydrogen atom or a methyl group;

R_3 represents a hydrogen atom when R_2 represents a methyl group or otherwise represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a methylthioalkyl group having from 2 to 5 carbon atoms or a dimethylamino group;

R_4 represents a hydrogen atom when R_3 represents a dimethylamino group or otherwise represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms or a methylthioalkyl group having from 2 to 5 carbon atoms; and

R_5 represents a hydrogen atom, with a sulphide of the general formula

$$CH_3—S—CHRCl \qquad II$$

wherein R represents a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms, thereby to introduce according to the following stipulations one or more methylthioalkyl substituents of the formula(e)

$$CH_3—S—CHR—$$

wherein R is as above defined:

(a) if R_2, R_3 and R_4 all represented hydrogen atoms, for one of R_3 and R_4, both of R_3 and R_4 or all of R_3, R_4 and R_5,

(b) if R_2 represented a methyl group and R_4 represented a hydrogen atom, for R_4 or both of R_4 and R_5,

(c) if R_2 represented a methyl group and R_4 did not represent a hydrogen atom, for R_5,

(d) if R_2 and R_3 both represented hydrogen atoms and R_4 did not represent a hydrogen atom, for R_3 or both of R_3 and R_5,

(e) if R_3 represented a dimethylamino group, for R_5,

(f) if R_3 represented neither a dimethylamino group nor a hydrogen atom and R_4 represented a hydrogen atom, for R_4 or both of R_4 and R_5,

(g) if R_3 represented neither a dimethylamino group nor a hydrogen atom and R_4 did not represent a hydrogen atom, for R_5,

and either isolating the methylthioalkyltetracycline derivative or demethylthionating it by refluxing it in a solvent with Raney nickel to give the corresponding alkyl-tetracycline derivative (in which the or each alkyl substituent is of the formula RCH_2— wherein R is as above defined).

2. A process according to claim 1 in which the strong acid is sulphuric acid, methanesulphonic acid, hydrofluoric acid or trifluoroacetic acid.

3. A process according to claim 1 or claim 2 in which the reaction between the tetracycline derivative and the sulphide is carried out at from 0°C to 60°C.

4. A tetracycline derivative of the general formula I herein

wherein

R_1 represents a hydrogen atom, a hydroxy group or an acyloxy group having from 1 to 4 carbon atoms;

R_2 represents a hydrogen atom or a methyl group;

R_3 represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a methylthioalkyl group having from 2 to 5 carbon atoms or a dimethylamino group; and

R_4 and R_5 each represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms or a methylthioalkyl group having from 2 to 5 carbon atoms;

with the provisos that R_3 and R_4 do not simultaneously represent hydrogen atoms, that when R_2 represents a methyl group R_3 represents a hydrogen atom, that when R_3 represents a dimethylamino group R_4 represents a hydrogen atom and R_5 does not represent a hydrogen atom, and that when R_5 represents a hydrogen atom R_3 and R_4 do not represent

(i) a hydrogen atom and a butyl group respectively, or

(ii) a methyl group and a butyl group respectively, or

(iii) a methyl group and a hydrogen atom respectively.

5. A tetracycline derivative according to claim 4 in which R_1 and R_2 both represent hydrogen atoms.

6. A tetracycline derivative according to claim 5 in which R_4 represents a *t*-butyl group.

7. A tetracycline derivative according to claim 5 in which R_3 represents a dimethylamino group.

8. A tetracycline derivative according to claim 4 in which R_1 represents a hydroxy group and R_2 represents a methyl group.

9. 7 - Methylthiomethyl - 6 - demethyl - 6 - deoxy - tetracycline.

10. 9 - Methylthiomethyl - 6 - demethyl - 6 - deoxytetracycline.

11. 7,9 - Di - methylthiomethyl - 6 - demethyl - 6 - deoxy - tetracycline.

12. 9 - Methyl - 6 - demethyl - 6 - deoxy - tetracycline.

13. 7,9 - Dimethyl - 6 - demethyl - 6 - deoxy - tetracycline.

14. 7 - Methylthiomethyl - 9 - *t* - butyl - 6 - demethyl - 6 - deoxy - tetracycline.

15. 9 - Methylthiomethyl - α - 6 - deoxy - 5 - hydroxy - tetracycline.

16. 9 - Methyl - α - 6 - deoxy - 5 - hydroxy - tetracycline.

17. N^2 - Methylthiomethyl - 7 - dimethylamino - 6 - demethyl - 6 - deoxy - tetracycline.

18. N^2 - methyl - 7 - dimethylamino - 6 - demethyl - 6 - deoxy - tetracycline.

19. A tetracycline derivative of the general formula I prepared by a process according to any of claims 1 to 3.

20. A process for the preparation of a tetracycline derivative according to claim 4, the process being substantially as described in any one of the Examples.

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